Efficacy of the treatment with prostaglandin E-1 in venous ulcers of the lower limbs

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Background: **Venous ulcers represent an important medical problem because of their high prevalence and consequent sanitary costs. In this study, we evaluated the effect of prostaglandin E-1 (PGE-1), a drug that improves district ischemia, on the healing of venous ulcers.**

Methods: **We performed a randomized, placebo-controlled, single blind study in which 87 patients who had venous leg ulcers homogeneous for dimensions and characteristics were treated for 20 days with an infusion of prostaglandin E-1 or placebo, in association with topical therapy. The dimension and the number of the ulcers were determined at the beginning of the treatment and then every 20 days up to 4 months, or until total recovery. The main outcome of the study was the recovery percentage of the ulcers at the end of the 120-day period of observation and the referred healing time. The reduction in the extension of ulcers from the baseline measurement to the last observation was also evaluated.**

Results: **The baseline characteristics of the treatment and control groups were similar. The reduction in the size of the ulcers was faster in the patients treated with PGE-1. In this group, 100% of the ulcers healed ≤100 days, whereas in the placebo group, only 84.2% did so by the end of the 120-day observation period ($P < .05$). The estimated healing times of 25%, 50%, and 75% of the patients treated with PGE-1 were 23, 49, and 72 days, respectively, compared with 52, 80, and 108 for the patients in the placebo group. Only one serious event occurred in the treated group.**

Conclusions: **This study demonstrates the effectiveness of PGE-1 in reducing the healing time of venous ulcers, suggesting that venous ulcers should also be considered ischemic. (J Vasc Surg 2005;42:304-8.)**

Venous ulcers represent an important problem from both a medical and socioeconomic point of view. In fact, they have a prevalence of 0.25% to 1.25% in the general population because of their poor tendency to heal,[1-4] and the costs are high in terms of sanitary expenditure, invalidity, and absence from work.[5-7]

The origin of venous ulcers is controversial but certainly multifactorial.[8] On the one hand, they are closely related to hemodynamic disorders leading to venous hypertension and stasis[9,10]; on the other, they are connected with microcirculatory alterations, and in this context, the "fibrin cuffs" observed by Browse et al,[11] Burnard,[12] and Van der Scheur et al,[13] and the "white cells trapping"[14] described by Coleridge-Smith et al[15] and Thomas et al[16] certainly play a fundamental role. Whatever mechanism is responsible for the production and the evolution of venous ulcers, they are certainly the final expression of the upset of a metabolic and coagulative equilibrium involved in the maintenance of normal cutaneous trophism. A condition of chronic district hypoxia[17] breaks this equilibrium, leading to a cascade of events that produce the venous ulcers.

Previous studies demonstrated anti-ischemic effects of some drugs on venous ulcers.[18-24] Prostaglandin E-1 (PGE-1), a metabolite of the polyunsaturated dihomo-gamma-linoleic acid, is one of these drugs and plays a central role. It is not only a constituent of membrane phospholipids but it also acts mainly on membrane receptors on the intercellular adenyl-cyclase, producing a consequent increase in cyclic adenosine monophosphate that is able to carry out numerous actions, as reported in Table I.[25-35]

Table I. Pharmacologic effects of prostaglandin E-1

- reduction of the adhesiveness and platelet aggregation
- inhibition of the proliferation of the smooth muscle cells of the media
- reduction of the hematic viscosity
- profibrinolytic effect
- inhibition of the chemiotaxis and the activation of white cells
- restoration of the equilibrium between the microvascular flow regulating system and the microvascular defense system, with a reduction of the endothelial permeability and inhibition of the vasoconstrictive activity of thromboxane A2, serotonin, leukotrienes, and endothelin
- stimulation of formation and growth of collateral circulation

Starting from these assumptions, we conducted a study to determine if pharmacologic treatment with PGE-1, in association with elastic compression and local therapy, has a favorable effect on the healing of venous ulcers.

METHODS

Study design. In a randomized, single-blinded, placebo-controlled trial, we evaluated the effect of PGE-1 in reducing the healing time in 87 consecutive patients who had venous ulcers of the lower limbs without complications. The patients were randomized into two groups. The allocation sequence was obtained using a random-number

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The study was partially supported by a grant from University of Palermo.

Competition of interest: none.

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0741-5214/$30.00

doi:10.1016/j.jvs.2005.03.040

table (sealed envelopes). The treatment group (44 patients) was received PGE-1 (Prostavasin, Schwarz Pharma) at 60 mg/day in 250 mL of saline solution administered by venous infusion at about 120 mL/h (about 2 h/day) for 20 days. The placebo group (43 patients) received a venous infusion of a saline solution with analogous characteristics of duration and quantity.

Both groups were also treated with elastic bandaging and local therapy. The elastic bandaging was done with a short, stretch bandage applied with different levels of compression according to the different hemodynamic characteristics of the ulcers (depending on the prevalent alterations in the superficial or deep venous system). The bandage was 8 to 10 cm wide according to current guidelines.[36] Wound care consisted of regular ulcer cleaning with saline solution and topical antiseptics. The topical treatment was stopped after the complete cicatrization of the ulcers or after 4 months.

We were alert for the eventual insurgence of side effects during the entire period in which the treatment was administered.

The study complied with the Consolidated Standards of Reporting Trials (CONSORT) statement.[37] The protocol was approved by the ethics committee of the University Hospital "P.Giaccone" of Palermo, and all patients gave informed consent.

Patients. The trial enrolled patients who had venous ulcers of the lower limbs, which were defined as any nonhealing wound of the skin of the lower extremities caused by impaired venous return, without complications. The patients were between 37 and 75 years old.

The inclusion criteria were the presence of chronic venous insufficiency, evident clinically and with echo-Doppler evaluation; the presence of one or more ulcers for <1 year, with maximum orthogonal ulcer diameters having a product between 5 and 30 cm^2; an ankle-brachial index (ABI) ratio >0.90 for both limbs, and no contraindications for the use of PGE-1.

The exclusion criteria included evidence of arterial, diabetic, or neurotrophic ulcers and all of the possible pathologic conditions that cause peripheral ulcers, such as diabetes mellitus, hematologic diseases, neuropathy, arteriopathy, and vasculitis; active infection of the ulcers; saphenectomy or sclerotherapy during the last 6 months; ongoing treatment with heparin, antiplatelet drugs, heparinoids, other vasoactive drugs; and poor patient compliance.

Procedures, measurement, and outcomes. The patients were examined at the baseline visit and then after 20, 40, 60, 80, 100, and 120 days. They were followed as outpatients (the patients stayed in the hospital for about 6 hours and then went home).

A clinical examination and an assessment of the ulcers were performed at each visit. The number and the dimension of the ulcers were determined. The size of the ulcers was calculated from contour sheets at a central location by computerized planimetry using digital scanning and analysis software.

Before the study began, an ultrasound study of the lower limbs, according to current guidelines[38] was done on all the patients to determine the cause of the ulcers (varicose or post-thrombotic) and to exclude arterial alterations. An echo color Doppler machine (ATL HDI 1500, Bothell, Wash) with a 7.5-MHz linear probe was used. Arterial district evaluation of the lower limbs was performed with the patients in supine position; blood pressure at the ankle and the ABI index were measured according to the current Transatlantic Intersociety Consensus guidelines.[39] Venous district evaluation was performed with the patient in an orthostatic position to detect the presence of obstructive lesions (total or partial) and valvular insufficiency in the femoral, popliteal, and leg veins.

The outcome was the percentage of the ulcers healed at the end of the 120-day observation period and the referred time of healing. The reduction in the extension of the ulcers from the baseline measurement to the last observation was also evaluated.

Sample size and statistical analysis. The calculation of sample size for this trial was based on the assumption that the percentage of healed ulcers at the end of the observation period would be 80% in the placebo group. Based on 80% power to detect a significant difference ($P = .05$), we considered clinically relevant an increase of 25% in the rate of healed ulcers in the treated group; therefore, the number of patients to be randomized was 37 in each group.

The analysis of the efficacy endpoints was based on the intention-to-treat principle. Statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS) software version 11.0 for Windows (SPSS, Chicago, Ill). An unpaired Student's t test was used to compare continuous variables. The χ^2 square test and Fisher's exact test were used to compare differences between proportions. Time to recovery was evaluated with the Kaplan-Meier curve for cumulative ulcer healing over time.[40,41] The statistical comparison between the two groups regarding the healing time of the ulcers was done with the log-rank test.[41] Nonparametric data were evaluated by using median as measure of the center of the distribution and interquartile range (IQM) as measure of the spread. Statistical significance was stated for $P < .05$.

RESULTS

A total of 87 consecutive patients were enrolled from March 2003 to November 2003; 44 were randomized to the PGE-1 group and the remaining 43 to the placebo group. These patients were included in the intention-to-treat analysis. Nine patients (5 from the PGE-1 group, 4 from the placebo group) did not complete the study. Three withdrew consent, one from the PGE-1 group for the onset of gastrointestinal side effects, one from the placebo group for the onset of a cerebral stroke, and the remaining four missed the successive follow-up visits. Overall 78 patients (40 from the treatment group and 38 from the placebo group) completed the study.

As summarized in Table II, the groups were homogeneous for demographic characteristics, clinical history, ul-

Table II. Baseline patient characteristics

	PGE-1 group	*Placebo group*
Number of patients	44	43
Age, mean (SD)	53 (20)	57 (15)
Sex, female (%)	25 (56.8)	26 (60.5)
Clinical history, n (%)		
VTE	12 (27.3)	10 (23.3)
Sclerotherapy	9 (20.4)	7 (16.3)
Surgery	5 (11.4)	6 (13.9)
Duplex ultrasound findings, n (%)		
Total or partial obstruction	21 (47.7)	19 (44.2)
Superficial vein valvular incompetence	37 (84.1)	37 (86)
Deep vein valvular incompetence	23 (52.3)	21 (48.8)
Perforating vein valvular incompetence	25 (56.8)	21 (48.8)
Sapheno-femoral or sapheno-popliteal reflux	32 (72.7)	34 (79.1)
Concomitant conditions, n (%)		
Arterial hypertension	15 (34.1)	18 (41.8)
Obesity	14 (31.8)	14 (32.6)
Orthopedic diseases	8 (18.2)	6 (13.9)
Ulcer features		
Months from ulcer appearance, median (IQR)	5 (2-10)	5 (2-11)
Ulcer area, cm^2 (IQR)	13 (3-25)	11 (4-20)

PGE-1, Prostaglandin E-1; *VTE*, venous thromboembolism; *IQR*, interquartile range.

trasonography evaluation, size of the ulcers, type of local therapy, and associated disease.

Outcomes. A progressive reduction in the extension of the ulcerated wounds was observed in both groups up to complete cicatrization, which occurred in 40 patients of the PGE-1 group and in 32 patients of the placebo group. At the end of the 120-day observation period, the recovery percentage was 100% in PGE-1 group versus 84.2% in the placebo group, with a statistically significant difference ($P < .05$) in favor of the PGE-1 group.

As is summarized in Table III, these modifications happened in a shorter period of time in the patients treated with PGE-1 compared with the other group. After only 40 days, a complete cicatrization of the ulcers occurred in 42.5% of the patients in the treatment group, a percentage that increased to 67.5% after 60 days, to 85% after 80 days, and to 100% after only 100 days, before the end of the observation period. The process was slower in the placebo group, with a lack of complete healing after 4 months in seven patients (Tables III and IV).

Fig 1 shows the Kaplan-Meier curve for the cumulative healing of the ulcers over time. This shows that the estimated healing time of 25%, 50%, and 75% for the patients treated with PGE-1 was 23, 49, and 72 days, respectively, compared with 52, 80, and 108 for the patients in the placebo group, with a statistically significant difference in favor of the PGE-1 group ($P < .001$ by log-rank test).

The incidence of adverse events was 11.36% (5 of 44) in the PGE-1 group, and 4.65% (2 of 43) the in placebo group. Only one serious event (diarrhea and vomiting) occurred in the treatment group, such that the patient could not complete the study. The other side effects were headache (2 cases), hypotension (1), and nausea (1) in the PGE-1 group, and hypertension (1) and tachycardia (1) in the placebo group.

DISCUSSION

In this randomized study, the patients with venous ulcers were treated with PGE-1 in association with elastic compression bandage and topical therapy. Color flow Doppler scanning was used to ensure that only patients with "pure" venous ulcers were included. In fact, this method not only made it possible to evaluate the presence of valvular insufficiency related to primitive varices or post-thrombotic syndrome, but also allowed us to exclude ulcers that were ischemic in nature, connected with a reduction in district arterial flow and also through the Ankle Brachial Index. The 4-month observation time was sufficiently long enough to assess the long-term effects.[40,42]

The study demonstrated that the treatment with PGE-1 is effective on venous ulcers of the lower limbs. In fact, this treatment caused a quicker and more frequent healing, which took place for all the cases ≤100 days, before the last evaluation. Furthermore, the estimated healing time for 75% of the patients was 72 days for the group treated with PGE-1 versus 108 days for the placebo group, with a statistically significant difference in favor of the former group. These data are in accordance with those reported by Rudofski,[43] who demonstrated in a double-blind controlled study a complete healing of 40% of "resisting" ulcers in short times.

Still to be verified is the mechanism with which PGE-1 favors the healing of venous ulcers. Hemodynamic mechanisms linked to venous hypertension and stasis, on which PGE-1 does not seem to interfere, take part in the origin of venous ulcers. However, it is also true that other mechanisms that determine conditions of ischemic suffering are involved, such as the activation of the white cells, endothelial dysfunction, and the activation of fibrinogenesis, as well as changes to the cutaneous trophism. In the natural history of the venous ulcer, this is probably the pathophysiologic

Table III. Number of ulcers healed at various observations times*

	20 days (%)	*40 days (%)*	*60 days (%)*	*80 days (%)*	*100 days (%)*	*120 days (%)*
PGE-1 group	9 (22.5)	7 (42.5)	27 (67.5)	34 (85)	40 (100)	40/40 (100)
Placebo group	1 (2.6)	5 (13.1)	14 (36.8)	19 (50)	25 (65.8)	32/38 (84.2)

PGE-1, Prostaglandin E-1.
*Percentage of healed ulcers over all ulcers for each group.

Table IV. Ulcer area, expressed in cm^2, at various observations times*

	0 days	*20 days*	*40 days*	*60 days*	*80 days*	*100 days*	*120 days*
PGE-1	13.4 (3.2-25.7)	11.2 (2.9-22.3)	8.3 (3.1-17.1)	6.1 (2.7-12.1)	3.2 (2.0-8.6)	—	—
Placebo	11.7 (4.0-20.6)	10.1 (3.8-19.8)	9.7 (3.6-17.3)	8.9 (3.5-15.4)	7.1 (3.2-14.5)	5.3 (2.9-11.4)	3.9 (1.9-8.6)
P	NS	NS	<.05	<.05	<.05	—	—

PGE-1, Prostaglandin E-1; *NS*, not significant.
*Median and interquartile range and statistical significance.

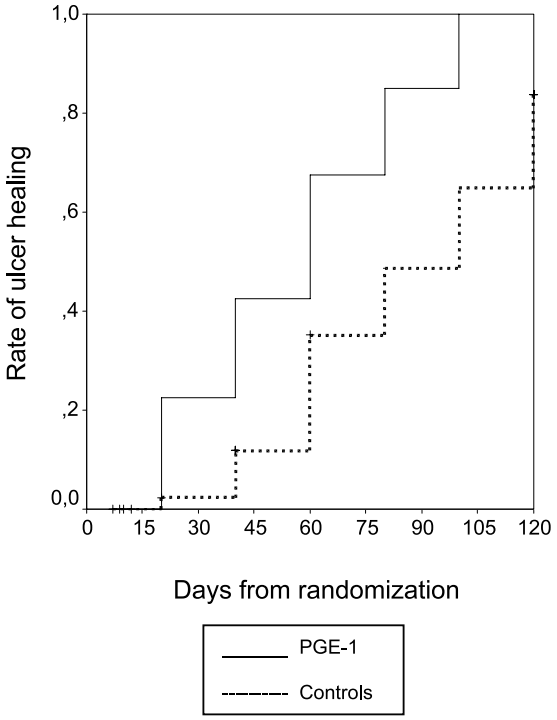

Fig 1. Kaplan-Meier curves for cumulative ulcer healing over time, including all randomized patients.

moment that can benefit more from treatment with PGE-1. This drug, among other actions, inhibits chemiotaxis and activation of white cells and is also able to stabilize the endothelial membrane and activate fibrinolysis, showing a favorable effect on the evolution of venous ulcers demonstrated in this research. Furthermore, such effect could also be related to the local improvement in microcirculation, as suggested by Rudofski.[43]

The long-term effects are more difficult to explain. In fact, one of the pharmacodynamic characteristics of PGE-1 is its poor stability and very brief half-life of about 30 seconds. This contrasts with the clinical efficacy that persists beyond its administration. This suggests that, on one hand, the effects could be related to one of its metabolites, PGE-0, that has a sensibly longer half-life and is biologically active with analogous efficacy. On the other hand, the explanation could be found in the numerous actions of PGE-1. In fact, if its direct effect on the vascular walls finishes in a few hours, the indirect effect on the fibrinolysis and the leukocytes lasts, longer causing part of the long-term effects.

Finally, PGE-1 treatment could assume a favorable cost-benefit ratio even though the economic cost is quite high. The reduction in the healing times should shorten the period of hospitalization and allow a quicker return to work, thus producing an improvement in the quality of life with positive socioeconomic reflections.[44] More studies performing a cost-benefit analysis are required to verify this hypothesis.

CONCLUSIONS

The data of this research demonstrate the effectiveness of PGE-1 in reducing the healing time of venous leg ulcers and support the idea that venous ulcers must also be considered "ischemic." Furthermore, the negative side effects of treatment with PGE-1 are, on the whole, acceptable and the drug is well tolerated by the patients.

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Submitted Oct 12, 2004; accepted Mar 30, 2005.